REMARKS

The specification has been amended to add a section entitled Brief Description of Drawings. Support for this amendment may be found in the specification at, for example, page 6, lines 23 to 36; page 7, lines 10-24; and page 7, line 25 to page 8, line 5 and in original drawings (Figs. 1-4). *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1565 (Fed. Cir. 1991).

The specification has been further amended to recite the full address of the international deposit authority, Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (DSM).

It is submitted that no new matter has been introduced by the foregoing amendments. Approval and entry of the amendments is respectfully solicited.

Election/Restrictions

On page 2 of the Office Action, the Examiner acknowledged applicants' election with traverse of Group II claims 9-16 in the response filed on May 1, 2008. (Paper No. 20080730 at 2). The Examiner acknowledged applicants' argument that the presence of both genes is disclosed to "improve the production efficiency of vitamin B_6 drastically, thus to require election between the two components of the recited vector would require Applicant to rewrite the claim in a fundamental way, which is not permitted." (*Id.* at 2) The Examiner further acknowledged that "no additional gene in the sense of pyridoxol 5'-phosphate synthase gene and D-erythrose 4-phosphate dehydrogenase gene needed to be selected" and that "both pyridoxol 5'-phosphate synthase gene and D-erythrose 4-phosphate dehydrogenase gene are under

examination." (*Id.* at 2) The Examiner, however, asserted that the reference to "specific genes" was actually reference "to a specific organism, for example, E. *coli.*" (*Id.* at 2) The Examiner concluded that "[c]laims 1-8 and 13-15 have been withdrawn from further consideration as being drawn to non-elected inventions" and that "[c]laims 9-12 and 16 are currently under examination." (*Id.* at 2)

We again respectfully request reconsideration of the species election requirement with respect to the specific genes. In this regard, we note that claim 9 is directed to a process for preparing vitamin B_6 using a recombinant microorganism engineered to contain a vector that encodes two specific genes, pyridoxol 5'-phosphate synthase (PNP synthase) gene and D-erythrose 4-phosphate dehydrogenase (E4P dehydrogenase) gene. The presence of both genes is disclosed to "improve the production efficiency of vitamin B_6 drastically ..." (page 2, lines 2-5), and as acknowledged by the Examiner, both genes are under examination. However, *S. meliloti* does not have an endogenous E4P dehydrogenase gene. As disclosed by the specification, in *E. coli*, E4P dehydrogenase is encoded by epd. (page 1, lines 12-14). Additionally, the specification discloses that

> according to [a] search of the genonme database of *S. meliloti* strain 1021, no homologue of epd of *E. coli* is detected. Furthermore, there has been no report about E4P dehydrogenase in *S. meliloti* so far. It is, therefore, considered that *S. meliloti* has [a] different biosynthetic pathway of HTP from that of *E. coli.* (page 1, lines 15-18).

In fact, the Examples disclose the use of *E. coli* E4P dehydrogenase in combination with *S. meliloti* PNP synthase. (Examples 1-5, pages 5-11). Therefore, to interpret the

election of genes as an election of genes from *S. meliloti* would require applicant to rewrite the claim in a fundamental way, which is not permitted. *See, e.g.*, 35 U.S.C. §§ 112 and 132 and MPEP 706.03(o). Thus, the species election is improper and should be withdrawn. Accordingly, we request that prosecution on the merits begin with respect to Group II (drawn to claims 9-16).

Objections

The specification was objected to for containing an "informality" in that it does not provide a Brief Description section to accurately describe each of the figures provided (Paper No. 20080730 at 3). As requested by the Examiner, the specification has been amended to add a section entitled Brief Description of Drawings. In view of the foregoing, it is respectfully submitted that the objection has been rendered moot and should be withdrawn.

We also note the Examiner's remarks regarding the use of multiple trademarks. It is believed that all of the trademarks are capitalized wherever they appear, and that they conform with the requirements with respect to the use of trademarks in specifications. If the Examiner believes otherwise, the Examiner is requested to specifically identify the deficiencies.

Claims 10-12 were objected to for containing an "informality" in that they "recite language of non-elected claims." (*Id.*) Claims 10-12 depend from claim 9, which is an elected claim, as confirmed by the Examiner. (*Id.* at 2) Therefore, in view of our comments above with respect to the election/restriction requirement, claims 10-12 are

not believed to recite language of non-elected claims. Accordingly, we respectfully request that the objection be withdrawn.

Indefiniteness Rejection

Claims 9-12 and 16 were rejected under 35 USC §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. (Paper No. 20080730 at 8-9). In making the rejection, the Examiner asserted that "[c]laims 11, 12 and 16 are rendered vague and indefinite by the use of the terms 'IFO 14782' and 'IFO 14782/pVK611'" (*Id.* at 8). The Examiner further asserted that "[i]t is unclear what is meant by said terms as no structural or biological properties are conveyed by said term." (*Id.*) The Examiner also questioned what constitutes "IFO14782" and "IFO 14782/pVK611" and whether they are "accession numbers or some other type of laboratory designation" (*Id.* 8-9). The Examiner concluded, "[a]s written, it is impossible to determine the metes and bounds of the claimed invention." (*Id.* at 9).

For the reasons set forth below, the rejection is traversed.

To reject a claim under the second paragraph of 35 USC 112, it is incumbent on the examiner to establish that **one of ordinary skill in the pertinent art**, when reading the claims in light of the supporting specification, would not have been able to ascertain with a reasonable degree of precision and particularity the particular area set out and circumscribed by the claims. *Ex parte Wu*, 10 USPQ2d 2031, 2033 (BPAI 1989). This, the Examiner has not done. The Examiner has not made any reasons or any factual determination that establishes that one of ordinary skill in the art

would not have been able to ascertain with a reasonable degree of precision and particularity the particular area set out and circumscribed by the claims based upon the terms "IFO14782" and "IFO14782/pVK611." (*Id.*) For this reason alone, the rejection cannot stand and should be withdrawn.

Furthermore, it is respectfully submitted that the metes and bounds of what is claimed are determinable with a reasonable degree of precision and particularity. In fact, one of the documents cited by the Examiner, Ichikawa *et al.*, EP 0765938 ("Ichikawa"), recites "IFO 14782". (*See e.g.,* Ichikawa, page 2, lines 46, 51, and 57; and Example 6). Furthermore, the Examiner herself recognized that IFO 14782 is a strain in the same Office Action in asserting that "Ichikawa et al. disclose that suitable **strains** include but are not limited to [*Sinorhizobium*] IFO 14782." (Paper No. 20080730 at 10, emphasis added).

With respect to IFO 14782/pVK611, the specification discloses that "*S. meliloti* IFO 14782/pVK611 were obtained by using *E. coli* HB101 carrying ... pVK611 as donor strains." (page 8, lines 29-31). Example 3 of the specification also discloses a method of introducing plasmids, such as pVK611, into *S. meliloti* IFO 14782 in detail. As for the contents of pVK611, Example 1 discloses the steps of cloning the two genes which are contained in pVK611, and Example 2 discloses the construction of pVK611, including parental plasmids used, the restriction sites, and the size of restriction fragments. (pages 5-8). Additionally, Fig. 4 shows the plasmid map of pVK611.

At bottom, there is nothing vague or indefinite about any of the recited terms "IFO14782" and "IFO14782/pVK611." One skilled in the art would readily recognize what is being claimed. Nothing more is required, and the Examiner has not

articulated any facts to support the rejection. Accordingly, it is respectfully submitted that the rejection should be withdrawn.

Written Description Rejection

Claims 11, 12 and 16 were rejected under 35 USC §112, first paragraph, as containing subject matter that was not described in the specification in such a way to convey that the inventors, at the time the application was filed, had possession of the claimed invention. (Paper No. 20080730 at 4-8).

In making the rejection, the Examiner asserted that "it is not clear that cell lines possessing the properties of ***Sinorhizobium meliloti*** **IFO 14782 and** ***Sinorhizobium meliloti*** **IFO 14782/pVK6** are known and publicly available or can be reproducibly isolated from nature without undue experimentation." (*Id.*) The Examiner further asserted that "[w]ithout a publicly available deposit of the above *Sinorhizobium meliloti* IFO 14782 and *Sinorhizobium meliloti* IFO 14782/pVK6, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of the cell line is an unpredictable event." (*Id.*)

As disclosed by the specification, *S. meliloti* IFO 14782 has been deposited under the terms of the Budapest Treaty with the Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (DSM) on September 4, 1995. (Page 3, lines 23-25). As noted above, the specification has been amended to recite the date of the deposit and the complete name and full street address of the depository. Furthermore, the undersigned, upon information and belief, states that the deposit has been accepted by the International Depository Authority under the provisions of the Budapest Treaty

and that all restrictions upon public access to the deposit, if there is any, will be irrevocably removed upon the grant of a patent on this application. Therefore, it is respectfully submitted that the rejection with respect to *Sinorhizobium meliloti* IFO 14782 has been rendered moot and should be withdrawn.

With respect to the rejection of *Sinorhizobium meliloti* IFO 14782/pVK6, we note that the specification discloses *Sinorhizobium meliloti* IFO 14782/pVK601, *Sinorhizobium meliloti* IFO 14782/pVK602, *Sinorhizobium meliloti* IFO 14782/pVK611. None of the rejected claims recite "*Sinorhizobium meliloti* IFO 14782/pVK6". Thus, the rejection is flawed as a matter of law and must be withdrawn.

In an effort to further prosecution, we assume that the Examiner intended "*Sinorhizobium meliloti* IFO 14782/pVK611" as recited, *e.g.*, in claim 16. As noted above, the specification discloses that IFO 14782/pVK611 is *S. meliloti* IFO 14782 comprising pVK611. (page 8, lines 29-31). The specification also sets forth the method of constructing pVK611. Example 1 discloses the steps of cloning the two genes which are contained in pVK611, and Example 2 discloses the construction of pVK611, including parental plasmids used, the restriction sites, and the size of restriction fragments. (pages 5-8). Additionally, Fig. 4 shows the plasmid map of pVK611. With the disclosure of methods of making pVK611, a person skilled in the art may readily construct pVK611. Furthermore, because *S. meliloti* IFO14782 is available to the public, IFO14782/pVK6 may also be readily reproduced in accordance with the methods disclosed in the specification. Accordingly, the specification discloses repeatable processes for obtaining the biological material. Thus, it is respectfully submitted that the written description rejection is rendered moot and should be withdrawn.

Obviousness Rejection

Claims 9-12 and 16 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Ichikawa *et al.*, EP 0765938 ("Ichikawa") and Yocum *et al.* (U.S. 2005/0164335 A1) ("Yocum"). (Paper No. 20080730 at 9-11).

The rejection respectfully is traversed.

Ichikawa discloses a process for producing vitamin B_6 by cultivating *Rhizobium* capable of producing vitamin B_6 and separating the resulting vitamin B_6 from the fermentation broth. (*See e.g.,* Ichikawa, Abstract).

Yocum discloses methods of producing B_6 vitaminers by culturing an organism overexpressing an enzyme in the B_6 vitamer biosynthetic pathway, mainly Type B pathway enzymes such as *YaaD* or *YaaE* gene products. (*See* Yocum, Abstract and Examples 2-9).

In making the rejection, the Examiner asserted that Ichikawa discloses "a process for producing vitamin B_6 which comprises cultivating a microorganism belonging to the genus *Rhizobium* (former name for *Sinorhizobium)* and being capable of producing B_6 in a culture medium under aerobic conditions and separating the resulting B_6 from the fermentation broth." (Paper No. 20080730 at 10). The Examiner also asserted that Ichikawa discloses similar culture medium pH, temperature, cultivation time and *Sinorhizobium* strains. (*Id.*)

The Examiner, however, acknowledged that Ichikawa does not "disclose that the claimed organism is transformed with a vector containing pyridoxol 5'-phosphate synthase gene and D-erythrose 4-phosphate dehydrogenase gene." (*Id.*)

To fill the knowledge gap, the Examiner relied on Yocum for disclosing "a method of producing B_6 vitamers." (*Id.*) The Examiner further asserted that Yocum's disclosed method "expresses pdxJ, which necessarily encompasses pyridoxol 5'-phosphate synthase gene and D-erythrose 4-phosphate dehydrogenase gene (see paragraph 0014)." (*Id.*) Additionally, the Examiner asserted that Yocum disclosed that "vectors containing genes encoding pdxJ are used (see paragraph 0015)." (*Id.*)

The Examiner then concluded that "[i]t would have been obvious for one of ordinary skill in the art at the time of the invention to transform *Sinorhizobium* with a vector containing pyridoxol 5'-phosphate synthase gene and D-erythrose 4-phosphate dehydrogenase gene because all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention." (*Id.* at 11) The Examiner also asserted that "[a]bsent evidence to the contrary the genes of the prior art are the same as those organisms recited in the instant claims." (*Id.*)

It is respectfully submitted that Yocum is not properly cited against the instant application. Initially, we note that the Examiner is citing the published U.S. application by Yocum *et al.*, with the publication date of July 28, 2005. We also note, however, that the instant application entered the U.S. national stage on September 9, 2005, but it was filed under the Patent Cooperation Treaty on September 16, 2003 and claims priority to European Application No. 02021621.4 filed on September 27, 2002. A copy of the European priority application is attached hereto as Exhibit A. The

specification of the European priority application is the same as the instant application. Therefore, the Applicants are entitled to the priority date of September 27, 2002, which pre-dates Yocum by more than two years. Accordingly, Yocum is not properly cited as prior art under 35 USC § 102(a).

Yocum is also not properly cited as a prior art under 35 USC § 102(e). Yocum claims benefit to a PCT application as well as several U.S. provisional applications, the earliest of which was filed on March 22, 2002. Therefore, at best, Yocum may be entitled to the March 22, 2002 U.S. provisional filing date as its effective filing date for prior art purposes. We note, however, that there are discrepancies between the benefit claim set forth on the face of the published U.S. application, the claim to benefit made in paragraph 0001 of the published U.S. application, and the published PCT application. Nonetheless, it appears that the March 22, 2002 provisional filing was followed up by three additional provisional filings (March 25, 2002, March 29, 2002, and March 3, 2003) and an international filing (March 21, 2003). For convenience, Yocum is attached hereto as Exhibit B, the March 22, 2002 Yocum provisional application is attached hereto as Exhibit C, the March 25, 2002 Yocum provisional application is attached hereto as Exhibit D, the March 29, 2002 Yocum provisional application is attached hereto as Exhibit E. In order for the published Yocum U.S. application to be effective as prior art under 35 USC § 102(e), there must be support for the allegedly patent defeating subject matter back to one of the March 2002 provisional filings ("March 2002 Yocum provisional applications") from which Yocum claims benefit. *See Transco Prods., Inc. v. Performance Contracting, Inc.*, 32 USPQ2d 1077 (Fed. Cir. 1994).

We note, however, that Yocum, lacks support in all three of the March 2002 provisional applications for the subject matter relied on by the Examiner to make the rejection. For example, the Examiner cited paragraphs 14 and 15 of Yocum as disclosing a method of producing B_6 vitamers expressing pdxJ and a vector containing genes encoding pdxJ. (Paper No. 20080730 at 10). The corresponding paragraphs appear on pages 3, line 36 to page 4, line 9 of all three of the March 2002 Yocum provisional applications. The table below compares these paragraphs in Yocum and in the three March 2002 Yocum provisional applications.

Yocum	March 2002 Yocum provisional applications
[0014] Yet another aspect of the invention features recombinant organisms, e.g., microorganisms which overexpress at least one Bacillus (e.g., B. subtilis) B6 vitamer biosynthetic enzyme (e.g., at least one of the yaaD, or yaaE gene products) or at least one of the epd, pdxA, pdxJ, pdxF, pdxB, pdxH, and/or dxs gene products, are described. In one embodiment, the recombinant microorganism is Gram positive (e.g., microorganisms belonging to the genus Bacillus, Cornyebacterium, Lactobacillus, Lactococci or Streptomyces). In another embodiment, the recombinant microorganism is Gram negative. Particularly preferred is a Bacillus recombinant microorganism (e.g., Bacillus licheniformis, Bacillus amyloliquefaciens, Bacillus subtilis, Bacillus pumilus, Bacillus halodurans, and the like).	Yet another aspect of the invention features recombinant microorganisms which overexpress at least one Bacillus (e.g., B. subtilis) B6 vitamer biosynthetic enzyme (e.g., at least one of the yaaD, or yaaE gene products) are described. In one embodiment, the recombinant microorganism is Gram positive (e.g., microorganisms belonging to the genus Bacillus, Cornyebacterium, Lactobacillus, Lactococci or Streptomyces). In another embodiment, the recombinant microorganism is Gram negative. Particularly preferred is a Bacillus recombinant microorganism (e.g., Bacillus licheniformis, Bacillus amyloliquefaciens, Bacillus subtilis, Bacillus pumilus, Bacillus halodurans, and the like).
[0015] Recombinant vectors that contain genes encoding Bacillus B6 vitamer biosynthetic enzymes, e.g., yaaD or yaaE genes, or homologues thereof, or epd, pdxA, pdxJ, pdxF, pdxB, pdxH, or dxs genes, or homologues thereof, are also described.	Recombinant vectors that contain genes encoding Bacillus B6 vitamer biosynthetic enzymes, e.g., yaaD or yaaE genes, are also described.

As shown in the table above, the corresponding paragraphs in the three March 2002 Yocum provisional applications do not disclose pdxJ (nor Epd, PdxA, PdxF, PdxB, PdxH, and Dxs, for that matter). Therefore, at a minimum, the evidence in Yocum the Examiner relied on post-dates the priority date of the instant application. As such, Yocum, as cited by the Examiner, also does not qualify as prior art under 35 USC § 102(e). For this additional reason, the rejection is deficient and should be withdrawn.

Furthermore, all other disclosures relating to pdxJ in the three Yocum 2002 provisional applications are either background information, relating to assessing whether certain organisms use the Type A pathway or the Type B pathway for vitamin B_6 synthesis, relating to *E. coli* lacking certain endogenous enzymes for the synthesis of vitamin B_6 (including pdxJ), or specifically relating to the overexpression of *E. coli* pdxJ in *E. coli* itself. None of the disclosures relates to the expression of *S. meliloti* pdxJ or *E. coli* pdxJ in *S. meliloti*. Accordingly, for this additional reason, Yocum is not properly cited against the instant application. Without Yocum, the Examiner cannot fill the factual gap left by Ichikawa, and therefore, the rejection should be withdrawn.

Furthermore, it is well settled that the Examiner bears the burden to set forth a *prima facie* case of unpatentability. *In re Glaug*, 62 USPQ2d 1151, 1152 (Fed. Cir. 2002); *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); and *In re Piasecki*, 223 USPQ 785, 788 (Fed. Cir. 1984). If the PTO fails to meet its burden, then the applicant is entitled to a patent. *In re Glaug*, 62 USPQ2d at 1152. It is also well settled that obviousness cannot be based upon speculation, nor can obviousness be based upon possibilities or probabilities. Obviousness ***must*** be based upon facts, "cold hard facts." *In re Freed*, 165 USPQ 570, 571-72 (CCPA 1970). When a conclusion of

obviousness is not based upon facts, it cannot stand. *Ex parte Saceman*, 27 USPQ2d 1472, 1474 (BPAI 1993). Further, "to establish *prima facie* obviousness of a claimed invention, ***all claim limitations must be taught or suggested by the prior art***." MPEP § 2143.03 (citing *In re Royka*, 180 USPQ 580 (CCPA 1974)) (emphasis added).

It is respectfully submitted that even if Yocum is properly cited against the instant application, which it is not, the Examiner failed to make a *prima facie* case of obviousness because she has not shown that all claim limitations are taught or suggested by the prior art. The Examiner asserted that Yocum discloses "pdxJ, which necessarily encompasses pyridoxol 5'-phos-phate [sic] gene and D-erythrose 4-phosphate dehydrogenase gene." (Paper No. 20080730 at 10) As support, the Examiner cited paragraph 14 of Yocum, which however, merely mentions pdxJ, but does not state that it "encompasses pyridoxol 5'-phos-phate [sic] synthase gene and D-erythrose 4-phosphate dehydrogenase gene." (*Id.*) Yocum, discloses that "the nucleotide sequence of pdxJ is set forth as SEQ ID NO:26." (Yocum, paragraph 27, last sentence). SEQ ID NO:26 of Yocum, when translated to amino acid sequences, reveals that it only encodes a pyridoxol 5'-phosphate synthase (or PNP synthase), <u>not</u> both PNP synthase and E4P dehydrogenase. (See Exhibit F for translation and Blast search results demonstrating that the polypeptide SEQ ID NO:26 encodes only the *E. coli* pyridoxol 5'-phosphate synthase). This is consistent with the disclosure of the instant application that only the PNP synthase is encoded by pdxJ gene. (Page 1, line 11). Thus, the Examiner failed to establish that Yocum discloses the genes for **both** PNP synthase and E4P dehydrogenase and, therefore, failed to establish that all

elements are disclosed by Ichikawa in combination with Yocum. As such, the rejection is deficient and should be withdrawn for this additional reason.

In view of the foregoing, it is respectfully submitted that the rejection has been rendered moot. Accordingly, withdrawal of the rejection is respectfully requested.

For the reasons set forth above, reconsideration, withdrawal of the gene election requirement, objections and rejections, and allowance of the claims are respectfully requested. If the Examiner has any questions regarding this paper, please contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on February 9, 2009.

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